By way of review, the present invention provides a quick and effective method for assessing in a patient whether there has been axonal damage resulting from a traumatic head injury (including stroke), and the extent of that damage. The assay method provides information both qualitatively (i.e., did the event occur?) and quantitatively (i.e., how severe was the event?). Until now, there has been no effective, minimally invasive procedure for quickly determining that information which, of course, can be critical in an emergency room setting. In this method, a patient suspected of having such traumatic head injury, such as a stroke or a blow to the head sustained in a car accident, provides a sample of cerebrospinal fluid. The presence in that fluid of specific tau proteins are then determined using a monoclonal antibody raised against those proteins, and the levels of those proteins in the fluid are compared to control samples representing both damaged and undamaged states. This comparison yields information regarding whether there has been a traumatic head injury and the extent of that injury in the patient.

The objections raised by the Examiner in the Office Action will now be considered sequentially, referring to the paragraph numbers used by the Examiner in the Office Action.

Paragraph 7. The Examiner has rejected claims 14, 17, 19-20, 23-24, 26-27, 29 and 32, under the first paragraph of 35 U.S.C. § 112, contending that the term "head injury" or "a method of determining axonal damage in the head" is not described in the specification and, in fact, is broader than what is described in the specification. That rejection is respectfully traversed by the Applicants. Initially, Applicants would like to point out that these terms are not used in claims 32 or 33 to define the scope of the present invention and so, in any event, this objection does not apply to claims 32 or 33.

The term "head injury" is in fact used in the present application, at page 1, line 9. The terms "head trauma" and "closed head trauma" are also used in the present application (see page 2, line 12 and 14, as well as page 3, line 5). Specific conditions which are encompassed within those terms are described in the present application at, for example, page 4, line 17 through page 5, line 4. The net result of all of this is that there is a clear basis in the present application for using those terms in the context of the assay defined in the present invention. Whether those terms are used in the application in the context of determining the presence of damage or to measure the extent of the damage, does not matter. The assay of the present invention does both a quantitative and a qualitative determination of head trauma in a patient and the terms objected to by the Examiner are clearly used in the context of describing the

utility of the present invention. Further, the term "traumatic head injury" is a term well known and well accepted in the art—see the attached materials from the U.S. Center for Disease Control and the Missouri Head Injury Advisory Council, which utilize and define the term. A PTO-1449 form listing those references is attached to this response. The terms "head injury" and "head trauma" are both described in the present application as defining the types of injuries which the assay of the present invention is used to measure; based on the attached materials, it is clear that they are fully equivalent to the well-known term "traumatic head injury" used in the claims. Accordingly, claim 14 and the claims dependent therefrom meet the description requirement of 35 U.S.C. § 112, and it is therefore respectfully requested that the rejection on that basis be withdrawn. Further, as discussed above, claims 32 and 33 do not utilize the objected to terms for defining the scope of the invention and, therefore, this objection does not apply to claims 32 and 33 in any event.

Paragraph 8. The Examiner has rejected claim 20, under the second paragraph of 35 U.S.C. § 112, as being indefinite for use of the phrase "said tau protein lacks the native N-terminal and C-terminal amino acids." The Examiner contends that these phrases are indefinite since one skilled in the art would not know exactly where the N-terminus or the C-terminus begins and ends in the molecules. The phrases "N-terminus" and "C-terminus" are very well known in the biotechnology arts. A quick computer search of the terms turned up literally thousands of instances of use without further clarification or description. Based on this, it is clear that one skilled in the biotechnology arts would understanding the meaning of claim 20, and it is therefore respectfully requested that the objection under the second paragraph of 35 U.S.C. § 112 be withdrawn.

Paragraph 9. The Examiner has rejected all claims currently pending in the present application, under the 35 U.S.C. § 102(b), as being anticipated by Vandermeeren et al. (WO 94/13795). Applicants respectfully traverse this rejection for the reasons given below.

Claim 32 is clearly limited to the determination of cerebrovascular accident (e.g., stroke). Vandermeeren et al. discusses Alzheimer's Disease and clearly has nothing to do with stroke or any other cerebrovascular accident. Accordingly, on its face, this rejection cannot apply to claim 32. Similarly, newly-added claim 33 relates to the use of the claimed assay to determine the presence of specific injuries: primary hemorrhage, primary vascular injury, traumatic lesions and acute cerebral vascular accident. Again, none of these conditions has anything to do with Alzheimer's Disease, and they are not in any way taught or suggested

in the Vandermeeren et al. application. Accordingly, this rejection cannot apply to claims 32 and 33 of the present application under any reasonable circumstances.

With regard to claim 14 and the claims dependent therefrom, those claims relate to an assay to detect the presence and extent of "traumatic head injury." "Traumatic head injury" is an art-recognized term which is defined as an injury caused by a sudden insult to the brain or head (see the attached excerpt from the Missouri Head Injury Advisory Council). Such injuries would include, for example, a head hitting the steering wheel of a car in a car accident, a head being hit by a baseball bat, or a bullet wound to the head. It very clearly would not include Alzheimer's Disease, which is not caused by a sudden insult to the head and therefore would not be considered a "traumatic head injury." If there is any doubt as to the correctness of that conclusion, the Examiner's attention is directed to the attached Missouri excerpt which expressly states that a "traumatic head injury" is "not of a degenerative nature." Since Alzheimer's Disease is degenerative in nature (see page 2, line 21 of the present application: "Alzheimer's Disease is a progressive degenerative disease..."), it clearly is not a "traumatic head injury." Since Vandermeeren et al. does not disclose or suggest any assays for traumatic head injuries, the present invention, as defined by the claims herein, is patentable over it. To support this position, Applicants have attached a Declaration Under 37 C.F.R. 1.132 of Dr. Joseph P. Broderick, the chairman of the Department of Neurology at the University of Cincinnati. Dr. Broderick, a well-known expert in the field of neurology and neurological conditions, states expressly that Alzheimer's Disease is degenerative and would not be considered a traumatic head injury. He further notes, in response to the Examiner's specific comments, that Alzheimer's Disease has very little effect on a patient's stability and so it would be very unusual for a traumatic head injury to be the result of a fall resulting from Alzheimer's Disease. In any event, the Vandermeeren et al. application says absolutely nothing about Alzheimer's Disease leading to falls and head trauma and, therefore, the Examiner's speculation in that regard is nothing more than that: pure speculation (and hindsight) without any basis in the art cited.

Based on the foregoing, it is respectfully submitted that the claims currently pending in the present application are patentable over the Vandermeeren et al. application and, therefore, it is respectfully requested that the rejection under 35 U.S.C. § 102(b) be withdrawn.

In light of the amendments and remarks herein, and the attached Declaration of Dr. Joseph P. Broderick, it is respectfully submitted that the present application is now in form for allowance. Accordingly, reconsideration and allowance of the currently pending in the present application are earnestly solicited.

Respectfully submitted,

Frank P. Zemlan et al.

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to The Assistant Commissioner for Patents, Washington, D.C., 20231, on

December 12, 2002

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Atty. Docket: 91830/0480191

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

Applicant:	Frank P. Zemlan et al.	: Paper No:	
Serial No.	09/035,708	: Group Art Unit:	1647
Filed:	March 5, 1998	: Examiner:	Robert C. Hayes, Ph.D.

For: METHOD OF DETECTING AXONAL DAMAGE, ASSOCIATED DISEASE STATES, AND RELATED MONOCLONAL ANTIBODIES AND PROTEIN CONTROLS THEREFOR

DECLARATION UNDER 37 C.F.R. § 1.132
OF JOSEPH P. BRODERICK, M.D.

The Assistant Commissioner For Patents
Washington, D.C. 20231

Dear Sir:

I, Joseph P. Broderick, M.D., do depose and say the following:

I am currently a professor and chairman of the Department of Neurology at the University of Cincinnati. I have been a practicing neurologist for 16 years and have expertise in the area of neurological diseases, neurological damage and assays for the measurement of neurological damage in patients.

My educational background is as follows:

I received my B.A. (summa cum laude) from Xavier University in 1978, and my M.D. degree from the University of Cincinnati in 1982. After graduation, I worked in the Mayo Clinic, from July 1981–June 1987, as a medical intern, a neurology resident, and a Fellow in Cerebrovascular Disease.

My experience as a neurologist is as follows:

I have served in various teaching and attending staff positions in the Department of Neurology at the University of Cincinnati from September 1987, through the present time. Among other positions, I was the Director of the Neurology Residency Training Program at the University of Cincinnati from May 1988 to July 1994. In September 1996, I was appointed Professor of Neurology and in April 2000, I was appointed Chair of the

Department of Neurology at UC. I continue to hold both positions at the present time. A copy of my full curriculum vitae is attached.

I am familiar with the above-captioned application and, specifically, with those portions of the Office Action, dated August 16, 2002, which rejected the above-captioned patent application based on PCT Published Application WO 94/13795 (Vandermeeren et al.). I have formed an opinion with regard to the Examiner's underlying basis for that rejection.

Alzheimer's Disease clearly would not fall into the category of traumatic head injury. "Traumatic head injury" is a phrase known in the art to refer to damage which is caused by a sudden physical insult to the brain or head of a patient, such as by a blow to the head. On the other hand, Alzheimer's Disease is a degenerative neurological disease and would not be considered a traumatic head injury under any circumstances.

In addition, a diagnostic assay for one disease involving the brain is not relevant for another brain disease for many reasons. For example, there are diagnostic tests for genetic markers of Huntington's Disease, a disease that involves neuronal degeneration. These tests would be completely inappropriate for Alzheimer's Disease, which also involves neuronal degeneration; they would not work. Also, multiple sclerosis is a disease that involves primary axons. A diagnostic test for multiple sclerosis (such as myelin basic protein) would not work for Alzheimer's Disease even though both involve axons, at least in part.

The processes of neuronal and axonal injury in acute head injury and Alzheimer's Disease are extraordinarily different. Alzheimer's Disease involves a very slow degeneration of the neurons, including the axons, over many years. It is not due to trauma and/or mechanical shearing of axons. In contrast, the injury to neurons, and particularly shearing of axons, from mechanical forces in acute brain injury happens over minutes to hours. The release of substances and the pathophysiology of the two processes are very different. Thus, the assay for the diseases would also be expected to be very different. Accordingly, the fact that the Vandermeeren et al. publication describes Alzheimer's Disease does not in any way suggest utility with regard to conditions resulting from head trauma. Further, there is no reason to believe, based on the teachings of Vandermeeren et al., that an assay which may be useful for diagnosing Alzheimer's Disease would in any way be useful for diagnosing the occurrence or severity of head trauma injury.

In response to the Examiner's speculation with regard to Alzheimer's Disease causing head trauma, Alzheimer's Disease, while affecting cognition of the patient, has little effect

upon gait stability except in the very latest stages of the disease. Almost no major traumatic brain injuries are thus due to falls which are secondary to Alzheimer's dementia, contrary to the suggestions of the Examiner.

In summary, Alzheimer's Disease does not involve traumatic injury to the axons in the brain and is not a significant cause of traumatic falls resulting in severe head injuries, except in very rare circumstances.

The information provided by me in this Declaration is true or, if based on information and belief, is believed to be true.

I understand that any willful false statements or the like made by me in this Declaration may result in invalidity of the present application or any patent issuing thereon, as well as fine or imprisonment or both, under 18 U.S.C. § 1001.

Further Deponent sayeth not.

11/24/02
Date

By _____
Joseph P. Broderick, M.D.

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